Clinical Genetics (continued)

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Male monozygotic twins discordant for Beckwith Wiedemann syndrome. ((N.J. Leonard and C.L. Johnson.)) Department of Genetics, Alberta Children's Hospital, University of Calgary, Calgary, Alberta, Canada.

A variety of abnormalities have been observed at chromosome 11p15.5 in conjunction with Beckwith Wiedemann syndrome (BWS). Duplications of paternal segments, paternal uniparental disomy and preferential maternal transmission all imply a role for imprinting in the etiology of BWS. The majority of clinical cases are recognized as sporadic but approximately 15% occur with autosomal dominant inheritance (incomplete penetrance/variable expressivity). Twin studies have shown that BWS monozygotic twins are frequently discordant. To date, 11 sets of twins have been described, 10 of which are female (9 are discordant) and one set of concordant male twins with a duplication of 15(q11.2,q13) mat. (Am J Med Genet 47:633, 1992; Am J Med Genet 45:S A75). Lubinsky and Hall (Lancet 337:1288,1991) have suggested that monozygous twinning may affect the expression of imprinting at the BWS locus resulting in discordance. It was suggested that, in view of the preponderance of female discordant twins, the phenomenon may be linked to the process of X-inactivation.

We report the first case of male monozygotic twins discordant for BWS. Twin A exhibited typical features of BWS including macrosomia, asymmetric growth, macroglossia, ear creases, glabellar nevus flammeus and neonatal hypoglycemia. Twin B had an entirely normal exam and an unremarkable neonatal course. Chromosomal testing revealed no visible aberrations of the BWS consensus region. Molecular testing has determined monozygosity, but has not defined a defect in the 11p15 region. Longterm follow-up of these boys has revealed comparable social and motor development. Twin A has maintained a significant growth differential but has experienced no medical difficulties to age 6 years. Further cytogenetic and molecular investigations are ongoing to evaluate this unique presentation of discordant BWS twins.

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Further evidence for a lethal X-linked syndrome of enteropathy, diabetes mellitus and endocrinopathy: DIETER syndrome. ((E. Levy-Lahad, R. Kapur and R. S. Wildin.)) University of Washington, Seattle WA.

Two maternal half-brothers had findings similar to an X-linked syndrome of diabetes mellitus (DM), polyendocrinopathy and fatal infection reported by Powell et al. (J Pediatr 1983;100:731). Both had bowel hypomotility, growth retardation, and thrombocytopenia. Pt. #1 was premature and had hypothyroidism. Pt #2, born at term, had neonatal DM. Both died of fulminant peritonitis at less than one month of age. On autopsy Pt.#1 had pancreatitis and islet cells were present. Pt. #2 had chronic pancreatic inflammation and no islet cells. In both there was diffuse erosion of the gut mucosa with absent crypts, reduced plica and no Paneth cells. The mother bore 3 healthy daughters between the births of the affected males.

In the Powell kindred, affected males usually died in infancy and had combinations of intractable diarrhea, DM, thyroid autoimmunity, hemolytic anemia, or eczema. Further evidence for this phenotype as a distinct clinical entity are reports of 2 families and 2 sporadic cases in which males died in infancy with neonatal DM with or without diarrhea. All infants with DM had pancreatic inflammation, and in most islet cells were absent. Pedigrees of the familial cases strongly support X-linked inheritance.

Linkage to the Wiskott-Aldrich syndrome (WAS) locus has been shown in the Powell kindred (Pediatr Res 1993;33:158A). An autoimmune pathogenesis is suspected, and our cases probably exemplify a progression from pancreatitis (in the premature pt.) to inflammatory islet cell destruction. Our family is unique in manifesting thrombocytopenia, suggesting this may be an allelic variant of WAS or a contiguous gene syndrome of WAS, the X-linked thrombocytopenia locus and an immune regulation locus.

We propose the mnemonic DIETER (Diabetes mellitus, fatal infection, Enteropathy, Thrombocytopenia, Endocrinopathy and Retarded growth) for this syndrome.

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Aplastic anaemia as a main referral for Fanconi Anaemia screening. ((J.C.Llerena Jr.[1]; S.Verma [2]; H.Galo [3]; J.C.C.de Almeida [1].)) (1) Centro de Genética Médica, IFF/FIOCRUZ; (2) Centro de Transplantes de Medula Óssea; (3) Inst. Estadual de Hematologia; Rio de Janeiro, Brazil. (Intro.by: Ieda Maria Orioli).

A regional Fanconi Anaemia (FA) registry was started in 1991 to collect clinical and cytogenetic data of affected individuals in the State of Rio de Janeiro (Brazil). 15 individuals from 13 families, including three sibs, were unequivocally diagnosed by MMC/DEB cytogenetic protocols. Our initial main goal was to identify among patients referred solely by the so called "idiopathic aplastic anaemia" (IAA) FA cases. Out of 16 cases with IAA, 9(56,25%) were diagnosed as FA patients. Comparatively, FA screening because congenital malformations (10), myelodyspàastic syndrome (5) and possible donors (4), 3(30%), 1(20%) and 2(50%-two sibs), respectively were considered affected. Consanguinity was present in two of the 9 FA with IAA. Cafe-au-lait spots were present in all affected FA individuals, however this feature was observed in 20% of non-affected cases. We observed a wide range of malformations already described in FA patients. however esophagic stenosis (1 patient) or pyloric stenosis (2 patients, including one female), periorbital hyperchromatic "rings"and a common facies, as previously reported by McDougall et al (Am J Med Genet 36, 408-413,1990), ocurred in at least three independent FA patients. The average age of diagnosis for the aplastic anaemia in affected cases was 5 years. The high frequency of FA patients among the IAA was not a surprise, as previously observed by Glanz and Fraser (J.Med.Genet 1982,19 412-416) and it may account for the underdiagnosis of FA cases.

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Clinical and genetic studies in dominantly inherited spinocerebellar ataxias (SCAS): analyses of clinical and genetic-heterogenity. ((I.Lopes-Cendes[1,2,3], E.Andermann[1,2], E.Attig[5], F.Cendes[4], J.Radvany[5], S.Bosch[7], M.Wagner[7], M.I.Botez[5], F.Gerstenbrand F[7], F.Andermann[5], G.A.Rouleau[1,2].)) 1.Centre for Research in Neuroscience, Montreal General Hospital, 2.Centre for Human Genetics, 3.Neurogenetics Unit, 4.Epilepsy Service, Montreal Neurological Institute and Hospital, 5. Hotel Dieu de Montreal, Quebec, Canada. 6. Neurologia Hospital, Israelite Albert Einstein, Sao Paulo, Brazil and 7.Department of Neurology, University Hospital, Innsbruck, Austria.

The SCAs are a clinical, heterogeneous group of neurodegenerative diseases. To date, two loci have been identified: one on chromosome (ch) 6p and one on ch 12q, the SCA-1 locus and the SCA-2 locus respectively. We have studied 4 large kindreds from different ethnic backgrounds segregating an autosomal dominant form of SCA. A total of 266 individuals, including 64 affected, were ascertained. We found marked clinical similarities among the 4 families. All kindreds showed progressive cerebellar ataxis, with a mean age of onset after the first decade of life.

We performed detailed clinical investigations and genetic analyses in these families in order to assess the clinical heterogeneity. In addition we correlated the results from these clinical studies with information from linkage analyses. Two of our families showed clear intrafamilial clinical heterogeneity, the Saskatchewan-Austrian (SA) and the Gaspé (O) kindreds. Neither anticipation phenomens nor sex influence could explain the clinical heterogeneity within each of these families. However, strong evidence for multiple modifier genes was found. The other two families the French-Canadian (FC) and the Brazilian kindreds (B), showed a more homogeneous clinical pattern. We have found that two kindreds which map to the SCA-2 locus, SA and O share certain clinical similarities such as age of onset range, and variable clinical evolution according to age at onset of symptoms. On the other hand, the remaining two kindreds: B which maps to the SCA-1 locus, and FC whose map position is still undetermined, have a more homogenous clinical presentation.

We have shown that, although there are marked clinical similarities among dominant SCAs from different ethnic backgrounds, certain clinical Differences can be detected, and these correlate well with the results of linkage studies.

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Natural history study of hereditary multiple exostoses. ((C. Luckert, R. Pauli, J.T. Hecht.)) Univ. of Texas Medical School at Houston, Univ. of Wisconsin at Madison.

Hereditary multiple exostoses (EXT) is an autosomal dominant disorder characterized by multiple bony protuberances usually arising in the juxtaepiphyseal region of the long bones. The purpose of the present study was to further delineate the natural history of HME. Forty-three probands and 137 of the affected relatives were included in the study. Approximately two-thirds of the probands had a positive family history. Penetrance was determined to be virtually 100%, in contrast to some previous studies that have reported reduced penetrance. Radiological examination and a careful family history are essential in determination of penetrance. Of the probands with a family history, there was a significantly higher number of affected males over females. However, in nuclear families (probands with a positive family history, affected siblings and parents), the male to female ratio was equal showing that there was no sex ratio skewing. These results suggests a possible bias in the ascertainment of the probands, with males in this group having more complications due to the exostoses and thus coming to medical attention more often than females. Short stature is a characteristic of EXT with 36.8% and 44.2% of adult males and females, respectively, falling below the 5th percentile in height. The mean number of exostoses excised for affected adults was 3.6 with the femur being the most commonly affected bone. Complications such as nerve compression, blood vessel compression and spinal cord compression were reported in 22.6%, 11.3% and 0.6%, respectively. These results suggest that nerve compression is more common than previously reported and spinal cord compression is extremely rare. Previous studies have reported cancer in as many as 25% of affected individuals. In the present study exostoses-related cancer was reported in 5 cases (2.8%) of all affected individuals with a mean age of diagnosis of 28 years. This result suggests that previous studies have overestimated the prevalence of cancer in EXT. The age onset of arthritis appears to be younger for individuals affected with EXT. Cesarean section appears to be two times more common in women with EXT.

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Age-at-onset effects of the (CAG)n repeat inherited from the non-HD parent: evidence for imprinting of the HD gene. ((JC MacMillan, R Snell, DJ Shaw, PS Harper.)) Institute of Medical Genetics. University of Wales College of Medicine. CARDIFF, UK.
There is significant correlation between age at disease onset and the degree of expansion of the (CAG)n repeat in the HD gene (IT15) in both maternally (r=-0.711, p<0.001) and paternally (r=-0.773, p<0.001) transmitted disease. There is however a stronger correlation in the age at disease onset between sibs who inherit the expanded (CAG)n HD allele from an affected father (r=0.645, p<0.001) than from an affected mother (r=0.362, p<0.001). We have shown that the length of the repeat sequence in the "non-HD" allele is also correlated with age-at-onset when the normal allele is paternal in origin (r=-0.290, p=0.015) but not when it is maternal (r=-0.145, p=NS). This suggests that there is differential expression of the non-HD allele depending on its parental origin.

Am J Hum Genet. 1993 Sep; 53(Suppl): 173–234. PMCID: PMC1682329

441/Th Trichorhinophalangeal syndrome associated with Wolff-Parkinson-White syndrome and other tachyarrythmias. M. Golabi,* M. E. Norton and R. Imagire.

442/W Simpson-Golabi-Behmel syndrome in a neonate: a second report of malrotation of the intestines. K. Grace* and E. H. Zackai.

443/Th Spinal cord compromise in Proteus syndrome. J. M. Graham, Jr.,* F. Skovby and M. M. Cohen, Jr.

444/W Phenotypic variability of ear malformations in dlastrophic dysplasia including one case of microtia/anotia. B. D. Hall.*

445/Th Neuroanatomic and cognitive outcome in school-aged children with achondroplasia. N. M. Thompson, J. Fletcher, W. A. Horton, T. Weir, T. Bohan and J. T. Hecht.*

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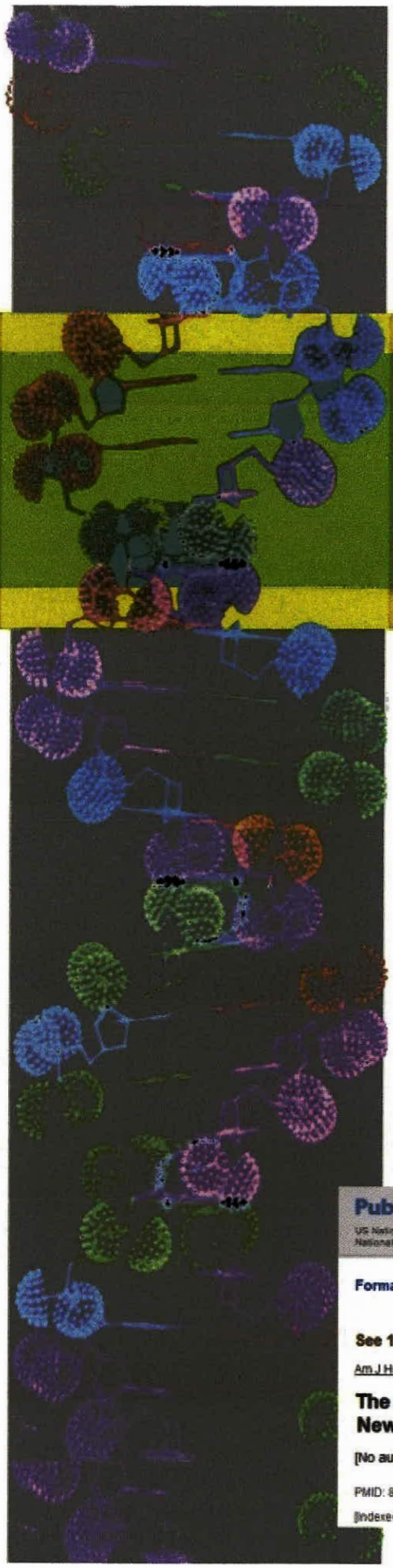

THE AMERICAN JOURNAL OF

HUMAN GENETICS

Volume 53, Number 3, September 1993

Supplement

PROGRAM AND ABSTRACTS 1993 ANNUAL MEETING

PUBLISHED MONTHLY FOR
THE AMERICAN SOCIETY OF HUMAN GENETICS
BY THE UNIVERSITY OF CHICAGO PRESS

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